DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/10 has been entered.

2. Currently, claims 1-8, 13, 16-83 are pending. Claims 1, 5, 13, 16, 32, 33, and 83 are under prosecution. All other claims are with drawn as being drawn to non-elected inventions.

3. Claim 16 is being considered only insofar as the second nucleic acid molecule is (ii), "a nucleic acid molecule comprising a nucleotide sequence complementary to the nucleotide sequence as set forth in SEQ ID NO: 7" All other possible molecules recited as the second molecule are withdrawn from prosecution as being part of non-elected combinations.

Claim Objections

4. Claims 16, 32, 33, and 83 are objected to because they recited non-elected subject matter in the alternative.

5. Applicant argues that the claims as presently presented reflect the elected subject matter since they all require SEQ ID NO: 7. However, applicant is reminded that the election of a particular combination of one or more sequences was required (page 6 and following of the restriction requirement mailed 4/14/06), and that in response applicant elected the combination

which includes the single sequence identified as SEQ ID NO: 7. Claim 16 is being considered only insofar as the second nucleic acid molecule is (ii), "a nucleic acid molecule comprising a nucleotide sequence capable of hybridizing to the complement of SEQ ID NO: 7…under high stringency conditions." Rejoinder of the additional combinations which require SEQ ID NO: 7 will be considered only when there are allowable claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 5, 13, 16, 32, 33 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims appear to be missing an essential step. For example, claim 1 recites in the preamble that it is "A method for determining the onset of colorectal adenoma" yet it includes only a single step of measuring the level of a expression of particular nucleic acid molecules. There is no step that actually results in the determination of the onset of colorectal adenoma. The examiner has suggested an allowable claim at the end of this office action. That claim is free of this problem.

Claim 1 recites "said individual" in line 8 of the claim but there is not proper antecedent basis for the word "individual." Amendment to recite "said human" would overcome this.

Claim 5 recites "said level of upregulation" in lines 1-2 of the claim but there is not proper antecedent basis for the phrase "level of upregulation." Applicant could correct this by amending the claim to recite "said increase in the level of expression."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 5, 13, 16, 32, 33, and 83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising

measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and

determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals,

does not reasonably provide enablement for methods which detect any other transcription or translation products, methods which utilize other samples, or methods for the positive detection of colorectal adenoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claim 1 recites a method for determining the onset of colorectal adenoma. Thus, the nature of the invention requires that the recited method actually determine the onset of colorectal adenoma.

Further, the claim encompasses "measuring the level of expression of (i) a nucleic acid comprising the nucleotide sequence as set forth in SEQ ID NO: 7 or (ii) a nucleic acid molecule comprising a nucleotide sequence complementary to the nucleotide sequence as set forth in SEQ ID NO: 7." "Measuring the level of expression" is understood in light of the specification to be a measurement of transcription or translation of a nucleic acid molecule- that is measuring mRNA products or measuring expressed protein products (p. 23 of specification). For this portion of the claim, measuring the level of expression encompasses measuring expression of an mRNA or protein product of any gene comprising SEQ ID NO: 7 or the complement of SEQ ID NO: 7.

Instant SEQ ID NO: 7 is a DNA sequence- so a nucleic acid molecule comprising SEQ ID NO: 7 is a DNA sequence. Instant SEQ ID NO: 7 is an approximately thirty-seven hundred base pair sequence. "A nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 7" includes, for example, the gene on a human chromosome which comprises SEQ ID NO: 7, no matter where the sequence occurs in the gene. Thus, the breadth of the claim encompasses measuring the level of expression of any transcript or protein that is expressed from a gene which comprises SEQ ID NO: 7, including, for example, the expression of mRNA transcripts that are

not actually complementary to SEQ ID NO: 7, provided that they were transcribed from a gene that comprises SEQ ID NO: 7. Likewise, the claim encompasses the detection of translation products that are not encoded by SEQ ID NO: 7 itself, provided they were translated from mRNA that were transcribed from a gene that comprises SEQ ID NO: 7. The claims do not actually require that SEQ ID NO: 7 be part of the detected RNA or that SEQ ID NO: 7 be translated to produce any polypeptide that is detected.

Claim 1 requires that the sample is a blood, serum, stool or gastrointestinal tract sample.

Claim 16 also is drawn to determining the onset of colorectal adenoma in a human, but the claim requires detecting the co-expression of two or more nucleic acid molecules in a blood, serum, stool or gastrointestinal tract sample from said human. At least one nucleic acid molecule comprises SEQ ID NO: 7, and, by election, the at least another nucleic acid molecule is a nucleic acid comprising a nucleotide sequence complementary to the nucleotide sequence as set forth in SEQ ID NO: 7. The scope of the claim is very similar to that set forth in claim 1, except that this claim requires that co-expression of two or more molecules be detected.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The dependent claims recites a further limitation, for example, wherein the level of upregulation is 10-100 fold the normal level (claim 5), wherein the subject of detection is the expression product of said nucleic acid sequence (claim 13), wherein the method is directed to monitoring for the onset or progression of said adenoma in said human (claim 32), wherein the sample is of colorectal origin or a biopsy sample (claim 33), and wherein the adenoma is a

tubular adenoma, tubulovillous adenoma, or a villous adenoma (claim 83), but all of these claims still encompass breadth and subject matter which is problematic and discussed in this office action.

The examples in the specification teach differential display analysis of samples of adenoma and normal tissue obtained from patients undergoing colonoscopy, comparison of the isolated sequences to nucleic acid databases housed by NCBI using BLAST, and RT-PCR confirmation of the differential expression of the isolated molecules (examples 1-3). Example 4 describes the testing of 71 colon adenoma tissue samples by quantitative RT-PCR and comparison of the expression levels to the mean expression levels of normal tissues. From these results a "fold increase" was tabulated for each isolated nucleic acid. The specification teaches on page 79, Table 2 that SEQ ID NO: 7 corresponds to Adenoma Marker clones named 12-2f and 8-2d.

Table 3 from the specification teaches that clone 8-2d was, on average, upregulated 50 fold relative to the mean expression levels of normal tissues, and that clone 12-2f was on average, upregulated 45 fold relative to the mean expression levels of normal tissues (table 3), and that both clones were upregulated greater than 5-fold in 100% of the adenoma tissues (table 5). The specification also teaches, however, that 19% of the normal tissue samples showed upregulation of both of these clones (table 6 and table 7).

There is no external working example which validates the use of SEQ ID NO: 7 as a marker for colorectal adenoma, but the declaration filed 3/26/10 provide data which validate the finding that SEQ ID NO: 7 has increased expression in colorectal adenoma colorectal samples versus healthy control tissue (see Exhibit 5, figure 5).

The data given in the tables is given as averages- the mean fold increase in adenoma samples versus the mean expression level of normal tissues. For both normal and adenoma means, no mention is given in the specification as to the ranges of observed values, the variation among samples or any formal statistical analysis to determine if the differences observed between types can be attributed to sample effects of to the chance of error. This is a significant absence given that the specification teaches that 19% of normal tissues also over expresses both clones, and because the claims positively state that they are methods for detecting the presence of onset of colorectal adenoma.

Since the breadth of the claims encompasses the detection of any mRNA transcript or encoded protein that is expressed from a nucleic acid comprising SEQ ID NO: 7, it is significant to note that the specification does not provide any evidence or guidance as to molecules that can be detected as differentially expressed other than the mRNA equivalent of SEQ ID NO: 7. There is no guidance as to what protein, if any is encoded by the mRNA equivalent of SEQ ID NO: 7 or by an nucleic acid which comprises SEQ ID NO: 7. In the declaration filed 3/26/10, applicant demonstrates in Figure 1, Exhibit 3, that instant SEQ ID NO: 7 occurs in an intron of gene KIAA1199. It appears, therefore, that the mRNA represented by the cDNA of SEQ ID NO: 7 does not encode any actual protein product. However, within the recitation of "detecting expression of a nucleic acid that comprises instant SEQ ID NO: 7," it appears that the claims as currently written encompass detection of a primary mRNA that encodes the KIAA1199 protein and also encompass detection of the KIAA1199 protein itself as indicators of the presence of colorectal adenoma. The declaration also teaches that there are multiple transcripts produced from the genomic region of human chromosome 15 that encodes KIAA1199 (see Exhibit 2 of the

declaration), and that SEQ ID NO: 7 is but one of these expression products (see paragraph 7), but the specification provides no guidance as to the identity of these transcripts, what proteins or protein fragments they encode, and which are differentially expressed relative to normal tissue in colorectal adenoma tissue.

The specification exemplifies that clones 8-2d and 12-2f have levels of expression higher than five fold versus average expression in normal control tissue in 100% of adenoma tissues, but the specification does not demonstrate that high levels of expression could be observed in other types of tissues- blood or serum or stool- or even that if it were that it would indicate colorectal adenoma. The specification does not provide any guidance as to what expression products or mRNA products that would be expressed from a nucleic acid comprising instant SEQ ID NO: 7 but that do not include SEQ ID NO: 7 and would meet all the limitations of the instant broad claims where such a nucleic acid can be used to determine the onset of colorectal adenoma in any human by measuring elevated expression levels of the sequence.

The specification does not demonstrate the detection of SEQ ID NO: 7 translation products, nor does it demonstrate that these putative translation products are detectable at different levels that could be used as set forth in the claimed methods. In fact, it appears from the declaration, that the mRNA detected whose cDNA is disclosed as SEQ ID NO: 7 does not have an expression product, per se, since it is an mRNA that would have been transcribed entirely from an intron.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention commensurate in scope with the claims.

It is highly unpredictable which transcripts expressed from a nucleic acid molecule comprising SEQ ID NO: 7 will be differentially expressed in colorectal adenoma tissues. High expression of Prostate specific membrane antigen (PSMA) in more aggressive prostate cancer makes PSMA a potential diagnostic target for prostate cancer (Schmittgen et al., Int. J. Cancer, 2003, 107:323-329). PSMA has three alternatively spliced variants, PSM', PSM-C and PSM-D. When PSMA and the alternatively spliced variant levels were compared by qPCR methods in various samples of normal, benign, primary and metastatic tissues from much larger sample size of 72 patients, however, the results indicate complex and contradictory expression profiles of the splice variants quite different from the initial PSMA expression patterns (Table III). For example although PSMA mRNA levels were seen increased 3-fold in primary prostate tumor, bone and lymph node metastases samples compared to normal prostate it was not increased in liver metastases samples but in fact decreased slightly. Therefore an increased PSMA mRNA expression level may be a marker for prostate tumor, bone and lymph node metastases but not for liver metastases. Additionally, not all PSMA variant transcripts showed increased expression levels in prostate tumor as the splice variants PSM-D expression level is not increased but rather decreased. PSM-D mRNA level, on the other hand, is increased in other types of tissues such as bone and lymph node metastases samples. Therefore the art teaches the use of a marker for disease risk assessment is unpredictable depending on the variants, biological sample and sources, and types of neoplasm.

Because the claims encompass the analysis of translation products of nucleic acid molecules which comprise SEQ ID NO: 7 or translation products of nucleic acids that comprise the complement of SEQ ID NO: 7 while the specification provides only an example of the

analysis of mRNA levels by differential display and quantitative RT-PCR of an mRNA, presumably the RNA equivalent of SEQ ID NO: 7, it is relevant to point out the unpredictability as to whether or not a measure of any nucleic acid expression is indicative of the level of protein in a sample. First, it is noted that based on applicant's declaration, it appears that the transcript that applicant disclosed as detecting (i.e. consisting of the RNA equivalent of SEQ ID NO: 7) does not in fact get translated into a protein. Further, though, it is noteworthy that the post-filing art of Chan teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus it is unpredictable as to whether or not the results pertaining to nucleic acid expression, as presented in the instant specification, would be applicable to methods requiring or encompassing the analysis of a protein samples.

That is, there no guidance or showing that demonstrates the range of values observed in the adenoma versus normal samples, and the specification teaches that at least 20% of the normal samples overexpressed the subject clones. It is highly unpredictable, therefore, what level of expression of SEQ ID NO: 7 must be observed in order for one to successfully conclude that adenoma is present, as recited in the preamble of the claims. In order to use the claimed invention commensurate in scope with the claims one would have to undertake an extensive amount of unpredictable experimentation.

In order to practice the invention commensurate in scope with the claims, one would have had to determine whether or not SEQ ID NO: 7 encoded a protein product. One would have had to determine what gene SEQ ID NO: 7 was a part of, and which transcripts of that gene are

expressed. Of those transcripts, one would have had to determine which are differentially expressed in colorectal adenoma biopsies relative to healthy tissue. The prior art had demonstrated that even for "tumor markers" all transcripts of a particular gene are not necessarily diagnostic of disease or expressed with the same pattern. Further, one would have had to determine which tissues the transcript comprising SEQ ID NO: 7 and any other transcripts or proteins expressed from a nucleic acid comprising SEQ ID NO: 7 or the complement thereof are expressed in tissues other than tissue obtained from colonoscopy, and when expressed in these tissues, which expression levels remain indicative of colorectal adenoma. Further, since the claims state that they are directed towards actually detecting the onset of colorectal adenoma, and since the specification teach that at least 19% of healthy individuals overexpressed the transcript comprising the mRNA equivalent of SEQ ID NO: 7, extensive experimentation would be required to determine which levels of SEQ ID NO: 7 expression actually positively identify the presence of disease. The quantity of experimentation in this area is extremely large since there are significant number of parameters which would have to be studied. Furthermore, one would have to discover the expression product or products of SEQ ID NO: 7 or nucleic acids comprising SEQ ID NO: 7 and establish reliable methods of detection and that this product is in fact translated in patterns similar to the transcription patterns of the observed mRNA. This would require extensive experimentation and specific guidance, with many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps, which are not routine, and an artisan of skill would not have known at the time of invention.

In the instant case, as discussed above, in a highly unpredictable art where an increased expression of a DNA marker is asserted to be associated with colorectal adenoma, the specification provides minimal guidance for a specific example (the expression levels of two clones in colorectal adenoma tissue) and insufficient guidance to support the full scope of the claims which includes detection of a variety of possible transcripts and protein products, in a variety of possible tissue types.

Further, the prior art and the specification provides insufficient guidance to overcome the art recognized unpredictability of different expression patterns for splice variants. Therefore the use of splicing variants are unpredictable as marker sequences for colorectal adenoma in various tissues and sample sources. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Remarks

The rejection has been modified to address the amended claims.

Applicant traverses the rejection insofar as it applies to the amended claims.

The traversal has been carefully considered but is not persuasive.

There has been considerable discussion on this record as to the relationship between instant SEQ ID NO: 7 and a molecule referred to in prior and post-filing date literature as KIAA1199. Applicant has provided evidence to show that instant SEQ ID NO: 7 matches a

portion of human genomic sequence that occurs between exons 1 and 2 of the genomic KIAA1199 sequence based on the exon/intron designations defined by the NCBI database (see declaration filed 3/26/10, at paragraph 6). However, neither the declaration nor applicant's arguments address whether or not the database information used to make this determination was available before the filing of the instant application. Either way, this information is not disclosed in the specification, and is in fact supplementary to the specification. It does not flow from the teachings of the specification. Regarding MPEP 2164.05, it is noted that the guidance sets forth:

> "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention"

Applicants and the Pedersen declaration state that NCBI's "AceView database" discloses experimentally identified cDNA clones transcribed from intronic sequences, and that SEQ ID NO: 7 is simply another of such transcripts (declaration filed 3/26/10, at paragraph 7). However, it is noted that SEQ ID NO: 7 is a DNA sequence, so presumably it is a cDNA of such a transcript (which would be an mRNA).

The declaration states that the experimental data in Exhibit 3 are provided to show that SEQ ID NO: 7 is in fact a transcript of the KIAA1199 gene. Figure 1 in Exhibit 3 shows that RNA samples derived from exons 1 and 2 of the KIAA1199 gene, which flank SEQ ID NO: 7, show upregulation in colorectal neoplasia; these data are not relevant to the instant claims which are directed towards onset of colorectal adenoma. This figure does not provide any actual data

regarding expression of an mRNA which comprises SEQ ID NO: 7 or the complement of SEQ ID NO: 7, since SEQ ID NO: 7 occurs entirely within an intron of the KIAA1199 gene, as discussed in paragraph 7 of the declaration. Figure 3 shows the results from a PCR experiment with RNA extracted from colon tissue specimens using one primer from within SEQ ID NO: 7 and one primer from within KIAA1199 exon 2, and PCR products were observed. The declarant concludes, based on this result that "Clearly, SEQ ID NO: 7 is an integral part of the genomic sequence of KIAA1199, and KIAA1199 is transcribed with the SEQ ID NO: 7 sequence forming part of the mRNA (declaration, paragraph 10)." None of these experiments use guidance provided in the specification to make their points about the function of any molecule which comprises SEQ ID NO: 7 or the RNA equivalent of SEQ ID NO: 7.

First, it is noted that these data presented in paragraphs is all entirely supplementary to the instant specification. Second, as previously noted, it is not clear on this record how much of the data relied upon from the NCBI databases would have been available to one having ordinary skill in the art. Third, there is no discussion in the instant specification to suggest that instant SEQ ID NO: 7 is an intronic transcript of KIAA1199.

The instant claims encompass measuring the level of expression of a nucleic acid molecule comprising SEQ ID NO: 7 or the complement of SEQ ID NO: 7. The specification teaches that measuring the level of expression can include measuring transcribed sequences (i.e. mRNA) or measuring translation products. It is clear from the specification, and supported by examples in the declaration that mRNA comprising the RNA equivalent of SEQ ID NO: 7 or its complement was detected as being more highly expressed in colorectal adenoma tissues relative to healthy control tissue. There is no guidance in the specification to suggest that the mRNA

detected was longer than that given in SEQ ID NO: 7, and in particular, no exon sequence from KIAA1199 is given in the specification.

Applicants address the 112 1st paragraph rejection as it relates to several elements of the claimed method: the sample source, other SEQ ID NO: 7-related sequences, detection of a protein product, an determination of an increase in expression. Applicants' remarks are addressed in the order they are presented.

Sample source: Applicants argue that biomarkers which were initially detected in tissue samples, such as PSA, CEA, and CAI9-9 are also expressed in blood. Applicant argues that the notion that detection of a biomarker in tissue samples translates to detectable changes in blood or serum levels is well documented and amply supported by the art, and confirmation thereof would not require undue experimentation. This is attorney argument that is not further supported by evidence on the record. It is not a priori predictable which markers can be detected in the blood and which cannot. Each of the markers to which applicant refers is supported by extensive experimentation and data to support its use as a marker, experimentation and data which is absent here for fecal, blood, or serum samples.

Applicants further argue that they provide additional specific data showing upregulation in the level of expression of KIAA1199 in stool and plasma samples were obtained, relying on the declaration filed 3/26/10 authored by Pedersen. The data in the declaration show that KIAA1199 protein is upregulated in stool samples and serum samples (para 12 an following of declaration). There is not a nexus between this data and the teachings of the specification. In particular, the specification provides only a specific teaching that clones 12-2f and 8-2d (which

the specification teach correspond to SEQ ID NO: 7) were detected as upregulated. There is no teaching in the specification that coding portions of KIAA1199 were detected as upregulated, nor is there any suggestion in the specification that SEQ ID NO: 7 is a portion of the genomic sequence which encodes KIAA1199. Since instant SEQ ID NO: 7 only contains intronic sequence of the KIAA1199 gene, the mRNA disclosed as detected in the specification does not encode any portion of this protein. The data given in the declaration regarding the detection of KIAA1199 in blood samples is additional to the specification. Consequently, these data are not sufficient to support the claim portion wherein the sample is stool, blood or serum. The declaration states in paragraph 12 that "increased level of KIAA1199 mRNA transcripts would also have occurred in these stool samples as well." However, it is not known from the experiments which mRNA transcripts would have been detected, as the declaration has previously established that there are multiple mRNA transcripts. The specification only discloses a detection of particular clones which inherently correspond to an intronic portion of the gene, as established in the declaration.

Applicants point to the declaration at paragraph 13 and Exhibit 4 to support the assertion that one would have expected that gene expression which is altered in colorectal neoplasms would also be detectable in stool and blood samples. The declaration does not provide any direct evidence that detectable levels of an expression product from an mRNA corresponding to SEQ ID NO: 7 is detectable in blood and/or stool.

The declaration points to a post-filing date reference, Galamb et al., that reports a microarray analysis of mRNA from colorectal biopsy specimen and peripheral blood of the same patients. First, as noted, the reference was published many years after the filing date of the

instant application and cannot be properly used to establish that the claims were enabled at the time of filing. Further, however, the reference highlights that without unpredictable experimentation it is unclear whether a given transcript will have a regulatory pattern that is similar in blood and in the disease tissue. While the reference reports fifty-two genes that were upregulated in both biopsy specimen and peripheral blood of colorectal cancer patients, and three that were similarly downregulated, the reference also reports that in some transcripts the mRNA expression in blood changed in the opposite way compared with their levels in cancer tissue (see page 2841, second column and Table 3). Thus, this exemplifies that it would take significant and unpredictable experimentation to determine if any transcript comprising SEQ ID NO: 7 or expression of any nucleic acid molecule comprising SEQ ID NO: 7 or the complement of SEQ ID NO: 7 would be differentially expressed in the blood of patients having colorectal adenoma versus healthy controls, such that the a transcript comprising SEQ ID NO: 7 or the complement of SEQ ID NO: 7 could be used in a diagnostic method as claimed.

The declaration states on page 14 that it is the author's opinion that once an upregulated expression of a biomarker is established based on tissue biopsy sample, the experimentation involved in confirming that elevated expression can also be detected in stool and blood samples would be routine and not excessive. However, as demonstrated by the Galamb et al. reference, such a showing would remain highly unpredictable. Further, the experimentation involved would be substantial requiring obtaining tissue samples from many patients and controls and conducting experiments whose outcome is uncertain with regard to whether or not the gene would be differentially expressed in blood or stool.

Other SEQ ID NO: 7-related sequences: The scope of the claims has been modified by amendment, and the breadth of the pending claims is discussed in the modified form of the rejection. Applicant argues that it is believed that this portion of the rejection is obviated, however, the examiner does not agree for the reasons set forth in the rejection.

Detection of a protein product: Applicant reiterates that the specification clearly asserts that the altered levels of expression of a relevant nucleic acid molecule can be detected at both the mRNA level and the protein level. This is agreed, the specification does assert as much. The specification does not provide any guidance, however, as to what protein product might be detected when measuring the level of expression of "a nucleic acid molecule comprising the nucleotide sequence as set forth in SEQ ID NO: 7" or the complement thereof. Here, that is a significant lack of guidance, since applicant's post-filing analysis and declaration have shown that SEQ ID NO: 7 a cDNA transcribed from an "intronic" sequence- meaning- that there is no protein product expressed from SEQ ID NO: 7. The claim is sufficiently broad so as to encompass the detection of KIAA1199 protein only when one considers translation of mRNA molecules not disclosed in the instant application, and therefore not disclosed as being detected as differentially expressed.

Applicant argues that the data provided in Exhibit 4 of the Pedersen Declaration demonstrate the increased levels of the translation product of a SEQ ID NO: 7-containing gene was detectable in stool samples of patients with colorectal adenoma. As previously discussed in this office action, the results given in Table 4 of the declaration are not commensurate in scope with the guidance given in the specification. Applicant is reminded that "Evidence to supplement a specification which on its face appears deficient under 35 U.S.C. 112 must

establish that the information which must be read into the specification to make it complete would have been known to those of ordinary skill in the art (MPEP 716.09)." Further, specification must be enabling as filed (MPEP 2164.05) and here there is no guidance in the specification as to the identity of the protein product.

There is absolutely no data in the specification to support the position that there exists any differentially expressed translation product that is expressed from a molecule comprising SEQ ID NO: 7. There is not a single piece of guidance in the specification to lead one having ordinary skill in the art to the conclusion that one could measure the level of expression of a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 7 by measuring KIAA1199 protein. Further, there is no data or guidance in the specification to support the assertion that the mRNA whose expression was observed even results in a translation product. In fact, based on the declaration, it appears that the disclosed mRNA corresponding to the cDNA SEQ ID NO: 7 does not actually ever get translated into polypeptide sequence.

Determination of an increase in expression: The claims as written purport to determine the onset of colorectal adenoma in a human. The statements made on pages 26-31 of the remarks have been fully considered. The examiner understands that in any test there will be outliers and that one can change the cut-off of an assay to determine the specificity and sensitivity of an assay. Here, the specification provides clear guidance that an mRNA related to SEQ ID NO: 7 was detected as being upregulated in colorectal adenoma, and applicant states that with that knowledge it would have been routine at the time the invention was made to have determined appropriate cut-off levels to achieve a desired sensitivity and specificity of an assay. Applicant states that the purpose of the method is to provide an "indicative" guidance in relation

to whether an individual has developed adenoma. These remarks are persuasive in general, but the claimed method states in plain language that it is for "determining the onset of colorectal adenoma," and this is not suggestive of a method for "indicative guidance" but instead for an actual diagnosis of the presence of the disease. Thus, more particular guidance would be necessary as to how to actually determine that colorectal adenoma is present, as stated in the instant claims. The data provided in the declaration Exhibit 5 support the statements in the specification that instant SEQ ID NO: 7 is upregulated in colorectal adenoma relative to normal healthy colorectal tissue.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 5, 13, 16, 32, 33, and 83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of the claims is discussed in the previous rejection. The broad claims encompass methods which detect a transcript comprising the RNA equivalent of SEQ ID NO: 7 (which is adequately described) but also encompass the detection of any transcription or translation product expressed from a nucleic acid molecule that comprises SEQ ID NO: 7 or the complement of SEQ ID NO: 7. As previously noted, the claims are sufficiently broad so as to

encompass the detection of transcription products that do not actually contain sequence that is RNA equivalent of SEQ ID NO: 7, and the detection of proteins that are not encoded by the mRNA disclosed in the specification. The claims require that any molecule detected have a particular functional property, namely that it be expressed in the tested tissue in such a way that increased expression of the detected molecule would be indicative of the presence of colorectal adenoma. Here, the specification has not provided any description of the detection of molecules other than the RNA that comprises the RNA equivalent of SEQ ID NO: 7.

The specification provides the reduction to practice of a the detection of two clones the scope of the claims, namely 12-2f and 8-2d which the specification teaches as being disclosed in SEQ ID NO: 7. There are no drawings or structural formulas to depict other molecules that can be detected as transcription or translation products of a nucleic acid comprising instant SEQ ID NO: 7 or the complement of SEQ ID NO: 7. The specification teaches that clones 2-12f and 3-13e (SEQ ID NO: 47) overlap in part, but there is no disclosure that 3-13e was detected as over expressed in the assays disclosed in the specification. There is no art recognized correlation as to what transcription or translation products of a nucleic acid comprising instant SEQ ID NO: 7 or the complement of SEQ ID NO: 7 would function in the claimed method as markers of colorectal adenoma. Consequently, there is no information about which molecules, other than the mRNA comprising the RNA equivalent of SEQ ID NO: 7.

Without extensive further testing, there is no way for one having ordinary skill in the art to be able to identify, based on the description provided in the disclosure additional transcription or translation products that would be useful as targets for measuring expression in the claimed methods. Based on the lack of knowledge and predictability in the art, those of ordinary skill in

the art would not conclude that the applicant was in possession of the claimed genus of methods based on the disclosure of the single species which relies on the detection of an mRNA comprising the RNA equivalent of SEQ ID NO: 7.

Response to Remarks

Applicant states that the amendments are believed to have overcome this rejection. The rejection is modified to address the scope of the pending claims, and maintained.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 5, 13, 32, 33, and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Markowitz (US 2004/0038220).

The provisional application does not appear to provide basis for the instantly claimed invention. In particular, the examiner was not able to identify disclosure of SEQ ID NO: 7. If applicant is able to establish basis to the provisional application, this rejection will be withdrawn.

The declaration filed in response to the previous office action establishes that instant SEQ ID NO: 7 falls within an intron of the gene encoding a protein identified as KIAA1199. Thus, methods which detect the presence of this transcription or translation products of this gene which comprises SEQ ID NO: 7 fall within the scope of the instant claims.

Markowitz teaches a method comprising measuring the level of a marker they refer to as Coloup1. Markowitz teaches that the probe for ColoUp1 was designed to recognize transcripts corresponding to the gene KIAA1199 (¶ 0155). Markowitz teaches determining the expression patterns of ColoUp1 in normal colon tissue and colon neoplasms from 15 individuals with colon cancers and one individual with a colon adenoma. Thus, Markowitz teaches a method which meets the actual process steps of the claim. The claim includes a further "wherein" clause referring to an increase in the level of expression of said nucleic acid molecule, and this is a statement of an inherent property of the level of expression of KIAA1199. Nonetheless, Markowitz also teaches that no normal colon tissue expressed the gene, 13 of 15 colon cancers expressed it, and the colon adenoma tissue expressed it. The increase in expression is infinitely greater since no expression was observed in the normal tissues. Markowitz detects the transcript which is an expression product of the genomic sequence. There are only three types of adenomas and these are listed in claim 83. The practice of the claimed method, therefore would inherently detect one of these three.

5. Claims 1, 5, 13, 32, 33, and 83 are rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by WO 01/49879, Ørntoft et al. (as cited in IDS).

The provisional application does not appear to provide basis for the instantly claimed invention. In particular, the examiner was not able to identify disclosure of SEQ ID NO: 7. If applicant is able to establish basis to the provisional application, the rejection under 102(a) will be withdrawn.

The declaration filed in response to the previous office action establishes that instant SEQ ID NO: 7 falls within an intron of the gene encoding a protein identified as KIAA1199. Thus,

methods which detect the presence of this transcription or translation products of this gene which comprises SEQ ID NO: 7 fall within the scope of the instant claims.

Ørntoft et al. teach a method for determining the presence or absence of a biological condition in an animal tissue comprising collecting a sample comprising cells and assaying an expression level from a gene in a "second group," one of which is KIAA1199, wherein upregulation of the second gene indicates the presence of the biological condition. Ørntoft et al. teach that the biological condition can be a onset of gastro-intestinal tract adenoma (p. 8). Ørntoft et al. teach that KIAA1199 is a potential oncogene because it is up-regulated during the malignant progression of colorectal cancer from normal tissue (p. 14, p. 18). On page 92, Ørntoft et al. teach that KIAA1199 is absent in normal tissue but present in Duke's A, B, C, and D disease samples. The samples assayed were all from the sigmoid or upper rectum (p. 75). The increase in expression is infinitely greater since no expression was observed in the normal tissues. Ørntoft et al. detect the transcript which is an expression product of the genomic sequence. There are only three types of adenomas and these are listed in claim 83. The practice of the claimed method, therefore would inherently detect one of these three.

Conclusion

The following claim would be allowed if presented in response to this office action:

A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising

measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and

determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday or Tuesday from 8:30 AM until 5:00 PM, or on Wednesday from 8:00 AM until 1:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached by calling (571) 272-0731.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of

the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

April 15, 2010